The Role and Effect of Antimicrobial Stewardship Programs Within the Hospital and How Rapid Diagnostics Can Make an Impact

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:33797317">http://nrs.harvard.edu/urn-3:HUL.InstRepos:33797317</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
The Role and Effect of Antimicrobial Stewardship Programs within the Hospital and How Rapid Diagnostics Can Make an Impact

Janeen Robin Manning

A Thesis in the Field of Biotechnology

for the Degree of Master of Liberal Arts in Extension Studies

Harvard University

May 2016
Abstract

Rapid diagnostics paired with an active antimicrobial stewardship (ASP) can have a positive impact on patients and hospitals because it can provide pathogen identification and antimicrobial susceptibility results sooner allowing patients to be placed on appropriate antimicrobial faster than conventional methods. Antimicrobial resistance is a growing concern because antimicrobials are being overprescribed and there are few antimicrobials in development leaving physicians with minimal treatment options. ASPs are being formed within hospitals in order to help combat the growing antimicrobial resistance issue in order to reduce the overuse of antimicrobials.

A total of six recent peer-reviewed articles were reviewed and compared to each other in order to determine if rapid diagnostics and ASP can have a positive impact on reducing antimicrobial usage, decreasing time to pathogen identification, and reducing time to appropriate therapy. Overall hospital outcomes were also reviewed to determine if they can help reduce length of stay, decrease hospital costs and lower mortality rates.

Overall, the studies all showed a reduction in time to pathogen identification, time to antimicrobial susceptibility and optimal therapy. A majority of the studies showed a decrease in mortality, reduction in length of stay and decreased hospital costs. All of these studies showed that pairing rapid diagnostics with an active ASP can have a positive effect on patient care and improve hospital outcomes. Providing fast acting results to clinicians sooner can help patients receive appropriate therapy faster and
potentially discharge them sooner helping to reduce the risk of developing further infections and decreasing the risk of antimicrobial resistance for the patient.
# Table of Contents

List of Tables ........................................................................................................ viii

List of Figures ......................................................................................................... ix

I. Introduction .......................................................................................................... 1
   Antimicrobials ..................................................................................................... 1
   Antimicrobial Resistance .................................................................................. 3
   Common Types of Bacterial and Fungal Infections ....................................... 5
   Clinically Relevant Bacteria and Fungi .......................................................... 6
   Conventional Methods of Detecting Infections ............................................. 9
   Rapid Diagnostics for Detecting Infections ................................................... 10
   Antimicrobial Stewardship ............................................................................. 12

II. Materials and Methods ..................................................................................... 16
   MALDI-TOF Methods .................................................................................... 16
      Perez et al. Study 2014 (Perez, et al., 2014) ............................................ 16
      Huang et al. Study (Huang, 2013) ............................................................. 18
      Perez et al. Study 2013 (Perez K., 2013) .................................................. 19
   Film Array BCID Panel Methods ................................................................. 20
      Banerjee et al. Study 2015 (Banerjee R, 2015) ........................................ 20
Verigene Gram-Positive Blood Culture Assay (BC-GP) .................................................. 22
Sango et al. Study (Sango A, 2013) ............................................................................. 22
FISH Technology Methods ......................................................................................... 23
Koncelik et al. (Koncelink DL, 2016) ......................................................................... 23

III. Results .................................................................................................................. 25
MALDI-TOF Study Results ......................................................................................... 25
Perez et al. Study 2014 (Perez, et al., 2014) ............................................................. 25
Huang et al Study (Huang, 2013) .............................................................................. 27
Perez et al. Study (Perez K., 2013) ............................................................................ 28
FilmArray BCID Panel ............................................................................................... 29
Banerjee et al. Study (Banerjee R, 2015) ................................................................. 29

Verigene Gram-Positive Blood Culture Assay (BC-GP) ............................................ 32
Sango et al. Study (Sango A, 2013) .......................................................................... 32
FISH Technology Results ......................................................................................... 33
Koncelik et al. Study (Koncelink DL, 2016) ............................................................. 33

IV. Discussion ............................................................................................................ 35
Time to Pathogen Identification and Susceptibility .................................................... 35
Antimicrobial Stewardship Intervention and Appropriate Therapy ......................... 40
Key Hospital Outcomes (Mortality, Length of Stay and Hospital Costs) ................. 49
Conclusion ................................................................................................................ 56

vi
List of Tables

Table 1. Clinical and Treatment-Related Outcomes for MALDI-TOF Study by Perez, 2014 .................................................................................................................. 26
Table 2. Clinical and Treatment-Related Outcomes from MALDI-TOF Study by Huang, 2013 .................................................................................................................. 28
Table 3. Clinical and Treatment-Related Outcomes from MALDI-TOF Study by Perez, 2013 Study. .................................................................................................................. 29
Table 4. Clinical and Treatment-Related Outcomes from FilmArray BCID Study. ...... 31
Table 5. Clinical and Treatment-Related Outcomes from Verigene BC-GP Study. ...... 33
Table 6. Clinical and Treatment-Related Outcomes for FISH Study. ......................... 34
Table 7. Antimicrobial Stewardship Interventions for Perez Study ............................... 43
Table 8. Antimicrobial Stewardship Interventions for Huang Study ............................. 44
List of Figures

Figure 1. Genetic Mutation Causes Drug Resistance. ................................................. 3

Figure 2. Time to Pathogen Identification for all Studies.......................................... 37

Figure 3. Time to Pathogen Susceptibility................................................................ 39

Figure 4. Time to Optimal Antimicrobial Therapy...................................................... 41

Figure 5. Patient Mortality Rates.............................................................................. 51

Figure 6. Overall Length of Stay ............................................................................. 53

Figure 7. Hospital Costs........................................................................................... 55
Chapter I
Introduction

This section will provide information on different antimicrobials that are commonly used to treat multiple types of bacterial and fungal infections and what pathogens are typically responsible for these infections. It will mention the different methods that hospital laboratories use in order to identify what pathogens are causing these infections and how treatment is determined. This section will also highlight the current issue our society faces with antimicrobial resistance due to overuse of antimicrobials and how it can have a negative impact on future generation if this issue is ignored. Finally, it will mention how an antimicrobial stewardship committee and rapid diagnostic methods can play a role in reducing the risk of antimicrobial resistance.

Antimicrobials

Antibiotics and antifungals are drugs (such as penicillin and fluconazole) that act on different mechanisms within bacteria and fungi, which will affect the growth of the organism by either inhibiting future replication, or by causing cell death. Antibiotics and antifungals, also known as antimicrobials, are commonly used to treat both bacterial and fungal infections. Some of these infections can be minor such as minor skin infections, urinary tract infections and bacterial vaginosis. Other infections can be serious and life threatening, which include bloodstream infections, meningitis and pneumonia.
A large number of antimicrobials are consumed each year in the United States and worldwide. From 2000 to 2010, there was a 36% increase worldwide in antimicrobial consumption, with India, China and the United States being the top 3 consumers of antimicrobials in 2010 (Van Boeckel, 2014). Previous studies have shown that 20-50% of all antimicrobials that are prescribed in acute care facilities within the United States are either unnecessary or inappropriate (Dellit, 2007) (Camins, 2009). In some instances, physicians prescribe antimicrobials when they are not needed, for incidences such as a cold or stomach virus. Antimicrobials have no effect on viruses and therefore the individual does not need to be taking them. In certain countries (India and Brazil), antimicrobials are sold over the counter, which means anyone can purchase them and most likely the antimicrobials are used inappropriately. Overuse of antimicrobials is dangerous, and can eventually lead to life threatening issues and global pandemics.

Overuse of antimicrobials can have serious side effects, such as adverse drug reactions and an increase in the risk of Clostridium difficile infections (Hensgens, 2012). C. difficile is a bacterium that is commonly found in elderly communities and typically after an exposure of antimicrobials. It is responsible for 250,000 infections/year and 14,000 deaths/year within the U.S. (CDC, 2013). C. difficile is not resistant to the antimicrobials used to treat it, but is of high importance because C. difficile is resistant to many commonly used antimicrobials that are used to treat other infections (Hensgens, 2012). Commonly used antimicrobials, such as clindamycin, cephalosporins and fluoroquinolones, will kill most of the patients’ good gut flora, allowing C. difficile to infect the individual (Bartlett, 2008). C. difficile will replicate and can cause serious infections or death. Reducing the use of antimicrobials can have an impact on reducing
the number of incidences of *C. difficile* infections and decrease the rate of antimicrobial resistance.

Antimicrobial Resistance

Antimicrobial resistance is becoming a major threat; worldwide it is the second leading cause of death and the third in the United States (Spellberg, 2008). With the increased use of antimicrobials we are forcing antimicrobial resistance by selective pressure, gene transfer and/or mutations (Levy, 2004). When humans or animals are exposed to antibiotics, some of these bacteria will mutate in order to survive. This allows bacteria or fungi to become resistant to antimicrobials. If an individual contains both susceptible and resistant forms of bacteria over time, and under continued selection pressure (i.e. antimicrobial treatment), the resistant bacteria will out-compete the susceptible strains and multiply by the billions. See Figure 1.

**Figure 1. Genetic Mutation Causes Drug Resistance.**
This figure shows how one non-resistant bacteria can mutate its DNA, becoming resistant, and then pass this mutation along to other bacteria. When the bacteria are
introduced to drugs, only the resistant bacteria will survive and eventually multiply (CDC, 2013).

These resistant bacteria or fungi can then spread to other individuals either throughout the community (community acquired infections, CAI) or throughout the hospital (hospital acquired infections, HAI). Immunocompromised individuals are the most susceptible to these types of infections because their immune system is often weakened and cannot fight against the infections. Bacteria can be found on all types of surfaces and can survive for hours, if not days, if the surface is not properly disinfected. As an example, between October 2014 and January 2015, there was a major outbreak of carbapenem-resistant Enterobacteriaceae (CRE) at the UCLA health system, in which 7 people were infected and 2 patients died. This CRE outbreak was caused by a contaminated duodenoscope (Almario, 2015). Another example of how quickly resistant bacteria can spread is the 2011 outbreak at the National Institute of Health (NIH) in Bethesda, Maryland. During this time, 18 patients were infected with carbapenem-resistant *Klebsiella pneumoniae*; unfortunately 11 of the patients died (Snitkin, 2012). The NIH discovered that one of the patients was infected with this bacterium, which was spread to 17 other patients either through contact of contaminated equipment or possibly by the healthcare workers. These two examples show how quickly and easily antibiotic resistant organisms can be spread through a hospital.

With the increase in antibiotic resistant organisms worldwide, an increasing number of bacterial and fungal infections are becoming more dangerous because there are fewer antimicrobials available to treat the resistant organisms. Currently, there are only a few new antimicrobials in the pipeline to help fight some of these antimicrobial resistant
organisms. There needs to be more funding towards antimicrobial development in order to reduce the risk of antibiotic resistance, not only in the United States, but also worldwide (Spellberg, 2008).

Common Types of Bacterial and Fungal Infections

Skin and soft tissue infections (SSTIs) are infections that affect the skin or the layer of soft tissue located under the skin (Ki, 2008). These infections can occur when the skin barrier is punctured either by lacerations, during surgery, wounds, bites or burns. SSTIs are common in the emergency department of hospitals and approximately 7-10% of patients are hospitalized each year with SSTIs (Ki, 2008). SSTIs can be minor bacterial infections such as impetigo, boils, furuncle or carbuncle, but they can also lead to severe life threatening infections such as necrotizing fasciitis. The majority of SSTIs are caused by Staphylococcus aureus and Streptococcus pyogenes, however many other environmental bacteria can cause SSTIs (Todar, 2008). The etiology for SSTIs can be different between community-acquired infections and hospital-acquired infections. For HAIs in North America, approximately 40% were methicillin-resistant S. aureus (MRSA) and Beta-hemolytic streptococci appeared to be more prevalent with CAIs (Rennie, 2003).

Urinary Tract Infections (UTIs) are common infections in women, but many of them can be easily treated as an outpatient with common antimicrobials (Lee, 2007). Catheter associated urinary tract infections (CA-UTIs) are more complicated UTIs which account for approximately 40% of HAIs, and are the most prevalent HAI in hospitals.
(Lee, 2007). CA-UTIs are caused by the colonization of bacteria on the catheter tip. The most prevalent bacteria that cause CA-UTIs are typically *Escherichia coli* but other organisms such as *Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus epidermidis, Enterococci*, and *Candida* species can also cause CA-UTIs (Warren, 2001). When these CA-UTIs are left untreated they can lead to bloodstream infections, known as bacteremia.

Bloodstream Infections are the 10th leading cause of death within the United States (Wisplinghoff, 2004). The bloodstream is a sterile body site, meaning no bacteria or yeast should be found in the bloodstream of healthy individuals. If bacteria (bacteremia) or yeast (fungemia) are found in the bloodstream, the individual has an infection and needs immediate medical attention. If these infections are not treated in a timely manner the patient will most likely develop sepsis and die. Bloodstream infections can be caused by a number of different conditions, such as an untreated SSTI or infections after any type of surgery, urinary tract infection or insertion of a catheter, or other medical device.

Clinically Relevant Bacteria and Fungi

There are many bacteria and fungi which can cause infections in humans, which are important due to the associated serious health risks when left untreated. *Staphylococcus* is a genus of organisms consisting of Gram-positive cocci in clusters which are most commonly found in positive blood cultures (~50%) (Wisplinghoff, 2004). There are a number of different species that make up this genus. One species,
*Staphylococcus aureus*, can cause sepsis and other serious infections (Koncelik, 2016). Also included in the *Staphylococcus* genus is a group of organisms commonly known as coagulase-negative staphylococci which are normally found as skin flora on humans and do not often cause serious infections (Koncelik, 2016). *S. aureus* is a commonly found bacterial infection. More than 300,000 individuals contract *S. aureus* each year in the United States, resulting in over 12,000 deaths, and almost $9.5 billion in added hospital costs (Klein, 2007) (Noskin, 2005). *S. aureus* is concerning because it has become resistant to commonly used antimicrobials, such as methicillin and on rare occasions vancomycin (Tosh, 2013) (Friaes, 2015), and fewer antimicrobials are available to fight these resistant strains. In 2013, the Centers for Disease Control (CDC) placed methicillin-resistant *S. aureus* (MRSA) on the United States “serious threats list”, and vancomycin-resistant *S. aureus* (VRSA) on the United States “concerning threats list” (CDC., 2013).

Coagulase-negative staphylococci (CoNS) are the most common bacteria found in positive blood cultures because they are commonly found on the skin and are introduced during the blood draw which can happen due to improper cleaning of the skin prior to the blood draw. These organisms are typically non-life threatening and are known as contaminants, which typically do not require antimicrobial treatment or hospitalization. Being able to differentiate between *S. aureus* and coagulase-negative staphylococci is extremely important due to the treatment algorithms between the two; a person with *S. aureus* will need antimicrobial treatment whereas a coagulase-negative staphylococci most likely does not antimicrobial treatment. Being able to identify CoNS in a rapid manner can help clinicians and pharmacists either stop unnecessary antimicrobial
treatment or never start treatment, and also allows for discharge non-sick patients from the hospital sooner (Forrest, 2006).

*Enterococcus* is a genus consisting of organisms of Gram-positive cocci in pairs and chains, and the third most commonly identified organisms in bloodstream infections (Wisplinghoff, 2004). *Enterococcus faecalis* and *Enterococcus faecium* are the two most commonly found enterococci in bloodstream infections. It is important to differentiate between these organisms because *E. faecalis* are typically susceptible to commonly used drugs, such as ampicillin and are relatively easy to treat. *E. faecium* infections are becoming more resistant to a high number of antimicrobials, leaving little to no treatment options (Forrest, 2008). In the United States, vancomycin-resistant enterococci (VRE) infect 20,000 individuals each year and are responsible for 1,300 deaths. VRE were placed on the “serious threats list” in 2013 by the CDC because of the high prevalence and lack of additional treatment options (CDC., 2013).

Gram-negative bacteria are the fourth most commonly found group of organisms in bloodstream infections (Wisplinghoff, 2004). They have become extremely important over the past few years due to their increase of resistance. The most commonly isolated Gram-negative bacteria in bloodstream infections are *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter* species, *Serratia* species and *Acinetobacter baumannii*. The majority of these organisms have resistance to one or more commonly used antimicrobials making them hard to treat. Carbapenem-resistant *Enterobacteriaceae* (CRE) are on the CDC’s “urgent list” because they are a group of organisms, many of which are common pathogens such as *E. coli* and *Klebsiella* species, and are resistant to almost all available antimicrobials leaving minimal treatment options.
There are approximately 9,000 CRE infections each year in the United States, leading 600 deaths. Additionally, multidrug-resistant *Acinetobacter*, extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae*, and multidrug-resistant *Pseudomonas aeruginosa* are three groups of Gram-negative organisms listed as “serious threats” because of their resistance to multiple classes of drugs (CDC, 2013). Being able to identify and determine antimicrobial susceptibility of these Gram-negative bacteria in a rapid manner is helpful to the treating clinicians and their patients. Providing rapid, targeted antimicrobial therapy can help many of these patients recover more quickly, remove unnecessary antimicrobial treatment sooner, and reduce the risk of developing more resistant infections.

**Conventional Methods of Detecting Infections**

Conventional or gold standard methodologies are commonly used methods to identify pathogens and determine antimicrobial susceptibility in all clinical microbiology labs. With conventional methods, pure cultures are needed because many of the standard techniques used are based on phenotypic methods, therefore isolated organisms need time to replicate, which can take 12-48 hours (Bauer, 2014). Once there is growth, a Gram stain is performed, which is the first piece of information that a clinician will receive from the lab. It does not provide pathogen identification or susceptibility information, but rather informs the clinician of which general class of microorganisms the organism belongs to (such as Gram-positive cocci in clusters, Gram-negative bacilli, or yeast), which helps the physician select an empiric therapy. The next step is to identify the
organism and determine the antimicrobial susceptibility of the pathogen. This step can take an additional 24 to 48 hours.

Conventional methods have been used in the clinical microbiology labs for decades. However, these tests can take 2-3 days for an answer which means the patient could be on the wrong antimicrobial(s) for this extent of time, or perhaps not even have a bacterial or fungal infection (Bauer, 2014). These conventional methods have now become backup methods for new rapid diagnostic assays.

Rapid Diagnostics for Detecting Infections

A number of new rapid diagnostic tests have recently been introduced and are being used in clinical microbiology labs. The rapid diagnostic tests allow labs to report the results in 1-2 hours (2-3 days sooner than conventional methods), which in turn allows physicians and pharmacists to use targeted therapy significantly earlier in patient treatment. This improvement in therapy allows patients to be discharged sooner, reducing the risk of acquiring hospital-acquired infections and limiting antibiotic resistance development. Hospitals are finding that by pairing rapid diagnostic tests with Antimicrobial Stewardship Programs (ASP) there is a benefit not only to the hospital but also the patient (Bauer, 2014).

AdvanDx PNA FISH® (Peptide Nucleic Acid Fluorescent in situ Hybridization) tests have been on the market for over 10 years. This technology allows the clinical lab to report bloodstream infections 24-48 hours sooner than conventional methods. PNA FISH
was the first generation assay, in which pathogen identification for the most common bloodstream infections were identified in approximately 90 minutes. AdvanDx QuickFISH® is the second generation test, reducing the time to result to 20 minutes.

Another recently introduced rapid diagnostic test is the BioFire FilmArray® assay. This assay is a multiplex PCR assay, which can simultaneously identify a number of organisms together on one platform, along with a few pertinent antimicrobial resistance markers. Pathogen identification and resistance marker detection can be reported within 90 minutes of a positive blood culture. This assay differs from PNA FISH and the QuickFISH tests because the BioFire test offers pathogen identification and resistance markers on the same test. Resistance markers help physicians and pharmacists determine which antimicrobial to use. For example, a pathogen identification of *S. aureus*, while helpful, does not further guide the clinician’s antibiotic selection. As an example, the BioFire test enables the lab to know if the patient has a *S. aureus* infection and if that organism has the mecA gene which confers resistance to the methicillin class of antibiotics, allowing the physician to select appropriate therapy sooner.

Nanosphere Verigene BC-GP® and BC-GN® tests are similar to the BioFire FilmArray test. The Verigene BC assays are a multiplex genetic test providing both pathogen identification and the resistance marker information separated in two tests. A Gram stain of the positive blood culture bottle is used to determine the appropriate kit to use. If the Gram stain is Gram-positive, then the lab will use the BC-GP (Blood Culture-Gram-Positive) test, and if it Gram-negative, the BC-GN (Blood Culture-Gram Negative) test is selected. Verigene does not have a yeast assay on the market, therefore another
method would be needed for the identification of yeast. With the Verigene test it takes approximately 3 hours to report the results.

A new technology being adopted by a number of large hospitals is MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization-Time of Flight). This technology allows a large number of bacteria and fungi to be identified in approximately 5-60 minutes post sample preparation, depending on the sample type. This technology is beneficial because the system contains a large database, permitting clinical microbiology labs to identify a more expansive range of organisms compared to other rapid diagnostic tests. It is also faster and less expensive than the conventional methods. MALDI-TOF is a highly complex test requiring a highly trained technician and does not provide resistance marker information, like the BioFire and Verigene tests.

Antimicrobial Stewardship

The Antimicrobial Stewardship Program (ASP) is an initiative being adopted by hospitals in the United States, and in other countries including the United Kingdom, France and Denmark, to help improve patient care, reduce healthcare costs and decrease adverse effects associated with antibiotic usage. (Dodds Ashley, 2014). California is currently the only state which requires all acute care hospitals to adopt and implement an antimicrobial stewardship committee (Trivedi, 2013). Recently the Centers of Medicare and Medicaid Services (CMS) proposed a rule that all long-term acute care facilities (LTAC) in the United States must implement an antimicrobial stewardship program in
order to participate in Medicare (IDSA, 2015). With these new proposed rules and state mandates more hospitals are likely to adopt an antimicrobial stewardship program.

Antimicrobial resistance is a worldwide growing concern due to the over prescription of antimicrobials and the limited number of new antimicrobials in the pipeline, leaving physicians with minimal drug options when treating antimicrobial resistant infections. The CDC, along with other important government officials, including President Barack Obama, have recognized the need for monitoring the use of antimicrobials in order to help reduce the development of multidrug resistant organisms.

The CDC released a report on the Core Elements of ASPs in 2014 (Pollack, 2014). It described the most important elements to any ASP are leadership commitment, assigned accountability, drug expertise, action, tracking, reporting and education (Pollack, 2014). The first element of ASP is leadership commitment, which ensures the institution dedicates a team of experts to ASP, along with financial and Information Technology (IT) support. This team is typically comprised of clinical pharmacists, infectious disease physicians, clinical microbiologists and infection prevention personnel (MacDougall, 2005). Together they are able to assess each patient and determine the optimal treatment. They are also responsible for the reduction of antimicrobial usage and educating hospital staff on ASP and proper antimicrobial usage.

The second element is accountability, which means that a single person or group of people are responsible in ensuring the hospital staff is following rules and protocols to help reduce overuse of antimicrobials. Experience has shown that a physician or
pharmacist can be a prime candidate to lead the ASP. It is helpful if this individual has formal training in infectious diseases and/or antimicrobial stewardship (Pollack, 2014).

The third element of ASP is drug expertise, which is provided by including a dedicated pharmacist that can track antimicrobial use in the institution, and work with physicians to determine proper patient treatment. The pharmacist can then calculate a number of different metrics helpful to the hospital’s ASP, including overall antibiotic use and cost.

Action is the fourth core element of ASP. Action refers to the implementation of at least one program that will help improve patient care and reduce overuse and the unnecessary prescribing of antimicrobials. These actions can be as simple as “antibiotic timeout,” which forces clinicians to reassess all patients after 48 hours of treatment to assess if their current treatment is still appropriate given new information provided by the lab (Pollack, 2014).

Tracking is the fifth core element. This element is important to ASP because it allows the institution to monitor antimicrobial prescription instances and rates. It also tracks infection rates, such as *Clostridium difficile* infections, and resistance patterns, allowing for early outbreak notification.

Reporting and education is the sixth core element, which ensures that information is provided for institution employees. Reporting informs the doctors, nurses and hospitalists about current antibiotic usage and resistance patterns within the institution. Continuing education is provided to teach staff proper ways to treat patients and the
importance of ASP. Collectively these six core elements are a great initial start to an ASP.

This work will review a number of recently published articles that compare rapid diagnostics to conventional methods and ASP in order to show that rapid diagnostics paired with ASP can help improve patient care and hospital management. A few key metrics that will be reviewed are time to pathogen and susceptibility identification, time to targeted antimicrobial therapy, length of stay, mortality and hospital costs. In the presence of rapid diagnostics and an active ASP we should see an improvement in patient and hospital management, which will give further evidence that rapid diagnostics and ASP should be adopted in all hospitals worldwide.
Chapter II

Materials and Methods

This section will discuss the materials and methods that were used in each of the experiments. Here we highlight four different rapid diagnostic technologies; MALDI-TOF, FilmArray BCID panel, Verigene Gram-Positive Blood Culture Assay and FISH technology. Each experiment will be discussed in detail in order to understand what key metrics were being measured and how each experiment was set up in order to capture those key metrics.

MALDI-TOF Methods

Perez et al. Study 2014 (Perez, 2014)

The Perez et al. study conducted at Houston Methodist Hospital measured the clinical and economic benefits that rapid pathogen identification, susceptibility and real-time antimicrobial stewardship can provide for patients with bloodstream infections caused by multidrug resistant (MDR) and/or extended-spectrum beta lactamase (ESBL) producing Gram-negative bacteria. This study consisted of two arms; pre-intervention (pathogen identification and susceptibility was performed via conventional methods) and intervention group (rapid pathogen identification and susceptibility with real-time antimicrobial stewardship review for treatment options), and included only patients with
MDR and/or ESBL-producing Gram-negative bacteria. The pre-intervention group was from January 2009 to November 2011 and the intervention group was from February 2012 to June 2013.

The pre-intervention and intervention group blood samples were inoculated into standard aerobic and anaerobic bottles and incubated on the BACTEC FX™ blood culture system. Once the bottle was positive, a Gram-stain was performed, and the result was reported by the microbiology staff to the nursing units and the infectious disease physician if listed. For the pre-intervention group, the positive blood cultures were inoculated onto the appropriate agar plates and organism identification and susceptibility was performed by conventional microbiology methods, which included the ID/AST BD Phoenix™ system. These results were entered into the electronic medical records, but no further notification was given to the patient-care team.

The intervention group used a previously published MALDI-TOF validation protocol (by Wimmer, et al., 2012) for implementation in their lab. Using this protocol, the lab was able to run Gram-negative organisms directly from positive blood culture bottles. The lab performed MALDI-TOF four times a day (05:00, 10:00, 13:00 and 19:00 hours). Perez et al. also set up their antimicrobial susceptibility from positive blood culture bottles using the BD Phoenix. From February 2012 to October 2012, the microbiology lab would call one of the Infectious Disease (ID) Pharmacists with the organism identification and then make a second call once the susceptibility results were available. Results were reported 24 hours per day and 7 days a week for all hospitalized patients. In October 2012, the hospital converted to an electronic data system and the ID Pharmacists were notified electronically when results were available. In both cases, the
ID Pharmacists would contact the patient’s physician in order to discuss their patient’s results and best course of treatment.

Metrics measured in this study were time to identification and susceptibility results, time to effective therapy, time to antibiotic optimization, length of stay in ICU and in the hospital, all cause 30-day and 60-day mortality and hospital costs.

Huang et al. Study (Huang, 2013)

Huang et al. conducted a study at the University of Michigan Hospitals and Health System. It was a single-center, pre-post quasi study that took place from September 1, 2012 – November 30, 2012. Adult patients over the age of 18 years with a bloodstream infection were compared to similar patients over the same 3-month period from 2011.

Positive blood culture bottles were Gram stained and sub-cultured for the pre-intervention group. The Gram stain results were reported to the ordering clinicians and also placed into their electronic medical records. Organism identification and susceptibility was performed by VITEK-2 (bioMérieux). During this time the antimicrobial stewardship team (AST) did not intervene on positive bacterial cultures. They did intervene when yeast were present and when patients were on restricted antimicrobials. Real-time alerts to the AST were performed during the intervention group.

For the intervention group, positive blood cultures were Gram stained and sub-cultured. Gram stain results were reported to the ordering clinician and also placed in the
The sub-cultured plates were incubated overnight and MALDI-TOF was performed the following day. The real-time results were reported to an AST member for all positive blood cultures via electronic medical records and email. The AST member would then provide the clinicians with antimicrobial recommendations.

Metrics measured during the study included length of stay (hospital and ICU), 30-day all-cause mortality, microbiologic clearance, recurrent bacteremia within 30 days of discontinuation of therapy, 30-day readmission for recurrent bacteremia with the same pathogen, time to effective and time to optimal therapy were recorded.

Perez et al. Study 2013 (Perez, 2013)

Perez et al. conducted a study at The Methodist Hospital in Houston, Texas. It was a single-center, pre-post quasi pre-intervention study that took place from August 15, 2011 to November 30, 2011 and an intervention study February 1, 2012 to May 25, 2015, on patients 18 years or older with one or more blood cultures which contained a Gram-negative organism.

For the pre-intervention group, the Gram stain was reported to the nursing staff and the infectious diseases physician if there was one on file. The blood cultures were then inoculated onto the appropriate agar media and final identification and susceptibility was determined through conventional methods using the Becton Dickinson (BD) Phoenix system. Final results were reported into the electronic medical record without notification to the clinicians or nurses.
The intervention group also had the Gram stain results reported to the patient care team. If a Gram-negative rod was identified in the Gram stain, the lab then analyzed the sample using MALDI-TOF and set up was initiated for susceptibility using the BD Phoenix system. Results were reported 24 hours a day, 7 days a week to the on-call infectious diseases pharmacist. The infectious diseases pharmacist and treating physician would then decide on the best course of treatment for each patient. MALDI-TOF was run three times a day; 10:00, 13:00 and 19:00 hours.

Metrics measured in this study included time to final identification and susceptibilities results, de-escalation rates, time to active therapy, hospital length of stay, total hospital costs, and 30-day mortality rates.

Film Array BCID Panel Methods

Banerjee et al. Study 2015 (Banerjee, 2015)

The Banerjee et al. study conducted at the Mayo Clinic in Rochester, Minnesota was a prospective randomized clinical trial which compared three different arms; control group (received pathogen identification and susceptibility through conventional methods), rapid multiplex PCR (received rapid pathogen identification and antimicrobial resistance genes through multiplex PCR) and rapid multiplex PCR with Antimicrobial Stewardship (AST) (received rapid pathogen identification and antimicrobial resistance gene through multiplex PCR and with real time AST recommendations on treatments). This study design allowed Banerjee et al. to determine if rapid diagnostics provide better
clinical and patient care with conventional standards, or if rapid diagnostics alone or with real-time stewardship provides better outcomes. This study only looked at patients with positive blood cultures between August 2013 and March 2014.

For all groups, positive blood cultures were isolated onto agar media and these isolates were then placed onto a MALDI-TOF for pathogen identification. Rapid testing for methicillin resistance *Staphylococcus aureus* (MRSA) was performed on *S. aureus* colonies using the Alere PBP2a assay for rapid identification of MRSA. The baseline institutional antimicrobial stewardship requirements were in place for all groups, which consisted of having an Infectious Disease physician approval before using restricted antimicrobials, and weekday (Monday through Friday) prospective audit and feedback for certain inpatient antimicrobial prescriptions.

The FilmArray Blood Culture ID (BCID) Panel from BioFire Diagnostics was used for both intervention groups, and was performed on positive blood cultures 24 hours a day, 7 days a week. Results were reported to the patient’s treating team by telephone and entered into the electronic medical records. For the rapid multiplex PCR with Antimicrobial Stewardship group, an infectious disease doctor or pharmacist was also notified via telephone 24 hours a day 7 days a week in order to rapidly optimize patient therapy.

In this study, Banerjee et al followed the subjects for 30 days. The primary goal was to determine the duration of antimicrobial therapy within the first 4 days of enrollment. Secondary goals were to measure the time for a positive Gram stain to the first active antimicrobial therapy, time to the first appropriate antibiotic escalation or de-
escalation, proportion of contaminants that were not treated, time to pathogen identification, length of stay, mortality and costs per patient.

Verigene Gram-Positive Blood Culture Assay (BC-GP)

Sango et al. Study (Sango, 2013)

Sanger et al. conducted a pre-intervention / post-intervention study performed at the University of Florida Health in Jacksonville, Florida over a 13 month period. All patients with positive blood cultures which contained enterococci were included in the study, unless they had multiple organisms present, died before the culture results were available, or were included in other investigational protocols. The pre-intervention group was from February 1, 2012 – September 9, 2012 and the post-intervention was from September 10, 2012 – February 28, 2013.

A Gram stain was performed for the pre-intervention group on all positive blood culture bottles. These results would be reported to the patient’s nursing station via telephone and also placed into the electronic medical records. Conventional methodologies were used (not specified) to determine pathogen identification and susceptibility results which were reported using the electronic medical records as they became available.

A Gram stain was also performed on all positive blood cultures for the post-intervention group and telephoned to the nursing station for each patient. The BC-GP test was performed on all Gram-positive cocci 24 hours a day, 7 days a week. These
results were then paged to the antimicrobial stewardship team Monday through Friday during the hours of 07:30-17:00. The antimicrobial stewardship team would contact the treating physician with antimicrobial therapy recommendations.

This study had two objectives, the primary objective to determine if the BC-GP assay could improve time to appropriate therapy for patients with enterococcal bacteremia compared to conventional methods. Rapid identification of enterococcal bacteremia is important because of the prevalence of vancomycin-resistant *Enterococcus* (VRE). Many patients are treated with vancomycin as an empiric treatment and therefore rapid identification of the organism and susceptibility will help treating physicians and pharmacists alter therapy sooner. The secondary objective was to determine if the BC-GP assay could affect length of stay and hospital costs.

**FISH Technology Methods**

Koncelik et al. (Koncelik, 2016)

Koncelik et al. conducted a study at Winter Haven Hospital, a community-based hospital in Winter Haven, Florida. It was a 9-month study from April 2013 – January 2014. This study had two distinct arms; pre-implementation (conventional methods) and post-implementation (*Staphylococcus QuickFISH*) and was focused on patients with positive blood cultures which contained coagulase-negative staphylococci (CoNS). Coagulase-negative staphylococci are primarily contaminants found in blood culture bottles normally due to a contaminated blood draw. Many times patients are placed on
empiric therapy when blood cultures are drawn but most patients with CoNS in the positive blood cultures do not need treatment. The goal of this study was to rapidly identify CoNS from positive blood cultures in order to discontinue antimicrobial therapy and discharge patients sooner.

The pre-implementation group contained 36 patients from April – August 2013 and performed pathogen identification via conventional methods. Positive blood cultures were Gram-stained and treating physicians were notified of the results. The samples were inoculated onto the appropriate agar media for initial classification and a Staphaurex™ latex agglutination test was performed for further identification. Treating physicians were notified of the conventional pathogen identification.

The post-implementation group contained 26 patients from August 2013 – January 2014. Positive blood cultures were Gram-stained and then immediately following the Gram stain Staphylococcus QuickFISH was performed. Staphylococcus QuickFISH is a 20 minute assay that rapidly differentiates S. aureus and CoNS. Once the QuickFISH results were completed the treating physician was notified with both the Gram stain result and the QuickFISH result. QuickFISH was performed 7 days a week except during the hours of 12:30 am – 5:00 am.

The outcome measures collected in this study were length of time to pathogen identification, patient length of stay, days on treatment (vancomycin) and associated hospital costs.
Chapter III
Results

This section will give the overview of the different experiments that were performed with MALDI-TOF, FilmArray BCID panel, Verigene Gram-Positive Blood Culture Assay and FISH technology. The results will be discussed and specific key metrics, such as turnaround time to pathogen identification and susceptibility results, time to appropriate antimicrobial therapy, length of stay, hospital cost and in some instances patient mortality.

MALDI-TOF Study Results

Perez et al. Study 2014 (Perez, 2014)

This study reviewed 269 patients (157 in the pre-intervention and 112 in the intervention group) and showed a significant reduction in time to identification (40.9 vs 14.5 hours), susceptibility results (46.7 vs. 29.3 hours) and adjusted therapy (80.9 vs. 23.2 hours). Perez et al. also showed that integrating a real time antimicrobial stewardship review significantly reduced the average time to initiation of an active antimicrobial by 57.7 hours (89.7 vs. 32 hours). Providing rapid pathogen identification and susceptibility along with a real time antimicrobial stewardship review showed a significant reduction in inpatient mortality (18.5% vs. 8%), all-cause 30-day mortality
(21% vs. 8.9%) and all-cause 60-day mortality (30.6% vs 12.5%). Finally, Perez et al. was able to show a significant decrease in mean hospital length of stay (LOS) for inpatient survivors (23.3 vs. 15.3 days), hospital LOS after bloodstream infection (BSI) onset (16.2 vs. 10.8 days), ICU LOS (16 vs. 10.7 days), ICU LOS after BSI onset (12.5 vs. 7.3 days) and finally a reduction in hospital costs ($78,991 vs. $52,693). See Table 1 for the full list of the Clinical and Treatment-Related Outcomes.

Table 1. Clinical and Treatment-Related Outcomes for MALDI-TOF Study by Perez, 2014.

<table>
<thead>
<tr>
<th></th>
<th>Pre-intervention (n=157)</th>
<th>Intervention (n=112)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Culture Positivity</td>
<td>18.4 ± 15.4 hrs</td>
<td>19.1 ± 15.7 hrs</td>
<td>0.58</td>
</tr>
<tr>
<td>Pathogen Identification</td>
<td>40.9 ± 15.1 hrs</td>
<td>14.5 ± 12.3 hrs</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathogen Susceptibility</td>
<td>46.7 ± 12.9 hrs</td>
<td>29.3 ± 14.7 hrs</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Optimal Therapy</td>
<td>80.9 ± 63 hrs</td>
<td>23.2 ± 19.9 hrs</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient Mortality</td>
<td>29 (18.5%)</td>
<td>9 (8%)</td>
<td>0.02</td>
</tr>
<tr>
<td>30-Day all-cause Mortality</td>
<td>33 (21%)</td>
<td>10 (8.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-Day all-cause Mortality</td>
<td>48 (30.6%)</td>
<td>14 (12.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>23.3 ± 21.6 days</td>
<td>15.3 ± 17.3 days</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospital LOS after BSI onset</td>
<td>16.2 ± 17.7 days</td>
<td>10.8 ± 12.2 days</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>16 ± 19 days</td>
<td>10.7 ± 17.6 days</td>
<td>0.008</td>
</tr>
<tr>
<td>ICU LOS after BSI onset</td>
<td>12.5 ± 15.6 days</td>
<td>7.3 ± 9.4 days</td>
<td>0.004</td>
</tr>
<tr>
<td>Total Hospital Costs</td>
<td>$78,991 ± $90,106</td>
<td>$52,693 ± $83,526</td>
<td>0.002</td>
</tr>
</tbody>
</table>

This table shows both the clinical and treatment-related outcomes for the study. Pathogen identification, susceptibility and optimal therapy were measured from blood culture positivity. Data are numbers (%) or mean ± standard deviation. ICU = Intensive Care Unit. BSI = Bloodstream infections. LOS = Length of stay. (Perez, 2014)
Huang et al Study (Huang, 2013)

Huang et al showed a significant reduction in time to pathogen identification (84.0 vs. 55.9 hrs.), decreased time to effective therapy (30.1 vs. 20.4 hrs.) and optimal therapy (90.3 vs. 47.3 hrs.). Time to optimal therapy measured the time from the blood culture draw to the time the patient received appropriate targeted antimicrobial therapy. Time to effective therapy measured the time from the blood draw to the time an effective antimicrobial was prescribed which was based on the susceptibility patterns of each pathogen. They were also able to show a significant decrease in 30-day all-cause mortality (20.3% vs. 12.7%), significant reduction in ICU length of stay (14.9 vs. 8.3 days), however no significance was found with overall length of hospitalization (14.2 vs. 11.4 days). Huang et al noticed that recurrence of bloodstream infections by the same pathogen was lower than the intervention group (5.9% vs. 2.0%), but there was no significant difference in the 30-day hospital readmission rate (3.5% vs. 1.6%). The antimicrobial stewardship team made 210 therapy recommendations and 189 (90%) were accepted by the prescribers. See Table 2 for more information on the Clinical and Treatment-Related Outcomes of this study.
Table 2. Clinical and Treatment-Related Outcomes from MALDI-TOF Study by Huang, 2013.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention (n = 256)</th>
<th>Intervention (n = 245)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture positivity</td>
<td>30.1 ± 50.1 hrs</td>
<td>32.5 ± 61.0 hrs</td>
<td>.621</td>
</tr>
<tr>
<td>Pathogen identification</td>
<td>84 ± 70.4 hrs</td>
<td>55.9 ± 35.9 hrs</td>
<td>.001</td>
</tr>
<tr>
<td>Pathogen susceptibility</td>
<td>87.3 ± 45.9 hrs</td>
<td>76.9 ± 62.1 hrs</td>
<td>.51</td>
</tr>
<tr>
<td>Time to effective therapy</td>
<td>30.1 ± 67.7 hrs</td>
<td>20.4 ± 20.7 hrs</td>
<td>.021</td>
</tr>
<tr>
<td>Time to optimal therapy</td>
<td>90.3 ± 75.4 hrs</td>
<td>47.3 ± 121.5 hrs</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
<td>52 (20.3%)</td>
<td>31 (12.7%)</td>
<td>.021</td>
</tr>
<tr>
<td>Time to microbiological clearance</td>
<td>3.3 ± 4.8 days</td>
<td>3.3 ± 5.7 days</td>
<td>.928</td>
</tr>
<tr>
<td>Length of hospitalization</td>
<td>14.2 ± 20.6 days</td>
<td>11.4 ± 12.9 days</td>
<td>.066</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>14.9 ± 24.2 days</td>
<td>8.3 ± 9.0 days</td>
<td>.014</td>
</tr>
<tr>
<td>Recurrence of same BSI</td>
<td>15 (5.9%)</td>
<td>5 (2.0%)</td>
<td>.038</td>
</tr>
<tr>
<td>30-day readmission with same BSI</td>
<td>9 (3.5%)</td>
<td>4 (1.6%)</td>
<td>.262</td>
</tr>
</tbody>
</table>

This table shows both the clinical and treatment-related outcomes for the study. Data are numbers (%) or mean ± standard deviation. ICU = Intensive Care Unit. BSI = Bloodstream infections (Huang, 2013).

Perez et al. Study (Perez, 2013)

This study was able to show a significant reduction in the average time to final identification and antimicrobial susceptibility with the intervention group. There was also a significant decrease in the length of stay for the ICU and the hospital overall. The all-cause 30-day mortality rate was lower in the intervention group, but it was not significant. Finally, there was a significant difference in the average hospital cost per survivor. Each survivor in the intervention group showed a $19,547 cost savings when compared to the pre-intervention group. During the intervention period 246 therapy
recommendations were made to prescribing physicians, 225 (91%) of those were accepted. See Table 3 for more information on the Clinical and Treatment-Related Outcomes for this study.

Table 3. Clinical and Treatment-Related Outcomes from MALDI-TOF Study by Perez, 2013 Study.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention (n = 100)</th>
<th>Intervention (n = 101)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture positivity</td>
<td>15.1 ± 10.78 hrs</td>
<td>16.2 ± 13.2 hrs</td>
<td>.3</td>
</tr>
<tr>
<td>Pathogen identification</td>
<td>36.6 ± 15.3 hrs</td>
<td>11 ± 10.2 hrs</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Pathogen susceptibility</td>
<td>47.1 ± 13.7 hrs</td>
<td>24.4 ± 11.4 hrs</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Optimal Therapy</td>
<td>75 ± 48 hrs</td>
<td>29 ± 17 hrs</td>
<td>.004</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>11.9 ± 9.3 days</td>
<td>9.3 ± 7.6 days</td>
<td>.01</td>
</tr>
<tr>
<td>Hospital LOS after BSI onset</td>
<td>9.9 ± 7.1 days</td>
<td>8.1 ± 6.4 days</td>
<td>.01</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>7.3 ± 8.5 days</td>
<td>6.3 ± 8.7 days</td>
<td>.05</td>
</tr>
<tr>
<td>ICU LOS after BSI onset</td>
<td>6.1 ± 6 days</td>
<td>4.9 ± 6.7 days</td>
<td>.09</td>
</tr>
<tr>
<td>Total hospital costs</td>
<td>$45,709 ± $61,806</td>
<td>$26,162 ± $28,996</td>
<td>.009</td>
</tr>
<tr>
<td>All-cause 30-day mortality</td>
<td>5.6%</td>
<td>10.7%</td>
<td>.19</td>
</tr>
</tbody>
</table>

This table shows both the clinical and treatment-related outcomes for the study. Data are given as mean ± SD. LOS = length of stay, BSI = bloodstream infection, ICU = intensive care unit, TTP = time to positivity, ID = identification (Perez, 2013).

FilmArray BCID Panel

Banerjee et al. Study (Banerjee, 2015)

A total of 617 patients were included in this study; 207 were in the control group, 198 in the rapid multiplex PCR (rmPCR) group and 212 in the rapid multiplex PCR and Stewardship group. There were 54.8% Gram-positive bacteria, 32.6% Gram-negative
bacteria, 2% *Candida* species and 10.5% contained more than one organism. FilmArray BCID does not detect every bacterium that can be found in bloodstream infections, in this study 81% of the samples were detected with FilmArray BCID.

For subjects with organisms detected via FilmArray BCID, this study showed a significant decrease for time to pathogen identification for both the intervention arms when compared to the control group (22 vs. 1.3 hours). See Table 4 for data. The primary objective of this study was to determine antibiotic utilization within the first 4 days and determine if there was a difference between the test groups. Banerjee et al. found a statistical significance in the time to the first appropriate de-escalation among the Rapid Multiplex PCR + Stewardship group compared to the control and Rapid Multiplex PCR groups. De-escalation of treatment was defined as removal of 1 or more antimicrobial therapy that is not beneficial to the patient, or switching from a broad-spectrum antibiotic to a narrow-spectrum antibiotic. This is normally done when the pathogen identification and/or susceptibility results are completed. They found that with the influence of FilmArray and an active stewardship team they could significantly reduce the time to antimicrobial de-escalation (34 hours control vs. 38 hours rmPCR vs. 21 hour. rmPCR + S). They also found a statistically significant difference in time to first appropriate antimicrobial escalation between the control group and the Rapid Multiplex PCR + Stewardship group (24 vs. 5 hours). There was no statistical significance between the control group and only performing FilmArray BCID; the significance came when FilmArray BCID was combined with stewardship. Antimicrobial escalation with FilmArray BCID alone was still faster than the control arm, though it was not statistically significant.
Unlike some of the other studies that have been mentioned in the MALDI-TOF section, Banerjee et al. did not see a statistically significant difference in length of stay, 30-day mortality, or hospital costs. This could be due to the fact that their experiment was more tailored to measuring antibiotic utilization instead of length of stay, mortality and hospital costs. They also mentioned that most of these patients were most likely over-treated than undertreated and were receiving at least one antimicrobial at the time of enrollment. Their conventional methods also use rapid technology such as MALDI-TOF and the PBP2a testing for MRSA which is also another reason no significant difference was seen with the cost benefits, length of stay and mortality.

Table 4. Clinical and Treatment-Related Outcomes from FilmArray BCID Study.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total</th>
<th>Control (n = 207)</th>
<th>rmPCR (n = 198)</th>
<th>rmPCR + S (n = 212)</th>
<th>P Value for 3 Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen identification &amp; Susceptibility</td>
<td></td>
<td>22.3 h (17-28)</td>
<td>1.3 h (0.9-1.6)</td>
<td>1.3 h (0.9-1.3)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Time to 1st appropriate de-escalation</td>
<td></td>
<td>34 h (21-55)</td>
<td>38 h (22-66)</td>
<td>21 (7-37)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Time to 1st appropriate escalation</td>
<td></td>
<td>24 h (3-67)</td>
<td>6 h (2-36)</td>
<td>5 h (2-22)</td>
<td>.04</td>
</tr>
<tr>
<td>Length of stay (entire hospitalization)</td>
<td></td>
<td>8 d (5-15)</td>
<td>8 d (5-15)</td>
<td>8 d (5-16)</td>
<td>.60</td>
</tr>
<tr>
<td>30-day mortality</td>
<td></td>
<td>22 (10.6%)</td>
<td>20 (10.1%)</td>
<td>18 (8.5%)</td>
<td>.74</td>
</tr>
<tr>
<td>Overall hospitalization costs</td>
<td></td>
<td>$65,450</td>
<td>$66,887</td>
<td>$68,729</td>
<td>.78</td>
</tr>
</tbody>
</table>

This table shows both the clinical and treatment-related outcomes for the study. Data are given as median (IQR) unless otherwise stated. IQR = interquartile range (Banerjee, 2015).
Verigene Gram-Positive Blood Culture Assay (BC-GP)

Sango et al. Study (Sango, 2013)

Overall 74 patients were included in the study, 46 for the pre-intervention group and 28 for the post-intervention group. The rate of vancomycin resistant bacteremia was 37% in pre and 50% in post. This study showed that using the BC-GP assay lead to a significant 48% reduction in time to appropriate therapy (48.5 vs. 25.1 hours) as well as a significant 50% reduction in time to appropriate therapy for patients with vancomycin-resistant enterococci (VRE) (62.7 vs. 31.6 hours). There was a 53% reduction in time to appropriate therapy for patients with vancomycin-susceptible enterococci (VSE) but it was not significant (40.2 vs. 18.6 hours). For hospital length of stay, there was a 50% reduction (43.2 vs. 21.5 days) which was statistically significant. When deceased patients were removed, the LOS did not remain statistically significant. Lastly, this study showed a 59% decrease in hospital costs between the pre and post-intervention groups. This was statistically significant, even when deceased patients were removed. See Table 5 for more data. Overall, the BC-GP assay provides faster time to pathogen identification and susceptibility for enterococcal bacteremia compared to conventional methods (3.15 vs. 50.6 hours). This in turn with antimicrobial stewardship helps physicians and pharmacists determine appropriate treatment options sooner than conventional methods.
Table 5. Clinical and Treatment-Related Outcomes from Verigene BC-GP Study.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention (n = 46)</th>
<th>Intervention (n = 28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen identification &amp; susceptibility</td>
<td>50.6 h</td>
<td>3.5 h</td>
<td>NA</td>
</tr>
<tr>
<td>Time to appropriate therapy, All enterococci patients</td>
<td>48.5 h</td>
<td>25.1 h</td>
<td>.0054</td>
</tr>
<tr>
<td>Time to appropriate therapy, VSE patients only</td>
<td>40.2 h</td>
<td>18.6 h</td>
<td>.1145</td>
</tr>
<tr>
<td>Time to appropriate therapy, VRE patients only</td>
<td>62.7 h</td>
<td>31.6 h</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hospital LOS, all patients</td>
<td>43.2 d</td>
<td>21.5 d</td>
<td>.048</td>
</tr>
<tr>
<td>Hospital LOS, deceased patients removed</td>
<td>43.5 d</td>
<td>22.2 d</td>
<td>.141</td>
</tr>
<tr>
<td>Hospital Costs, all patients</td>
<td>$103,075</td>
<td>$42,346</td>
<td>.02</td>
</tr>
<tr>
<td>Hospital Costs, deceased patients removed</td>
<td>$99,333</td>
<td>$41,139</td>
<td>.047</td>
</tr>
</tbody>
</table>

This table shows both the clinical and treatment-related outcomes for the study. VSE = vancomycin-susceptible enterococci, VRE = vancomycin-resistant enterococci, LOS = length of stay (Sango, 2013).

FISH Technology Results

Koncelik et al. Study (Koncelik, 2016)

This study reviewed a total of 62 patients; 36 in the pre-implementation group and 26 in the post-implementation group with CoNS positive blood cultures. Koncelik et al. were able to show a 92% reduction in time to pathogen identification (17.16 vs. 1.47 hours) when QuickFISH was used compared to conventional methods. There was also a significant decrease in length of stay by 30% (4.89 vs. 3.44 days) and a 65% reduction for days on vancomycin (2.52 vs. 0.89 days) when QuickFISH was used compared to
conventional methods. See Table 6 for more data. Winter Haven was also able to estimate a cost savings of more than $750,000 for the year if QuickFISH was used due to shorter length of stay and reduced use of vancomycin.

Table 6. Clinical and Treatment-Related Outcomes for FISH Study.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-intervention (n = 36)</th>
<th>Intervention (n = 28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen identification</td>
<td>17.16 h (5.5-43)</td>
<td>1.35 h (0.3-3.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patient LOS</td>
<td>4.89 d (1-10)</td>
<td>3.44 d (1-9)</td>
<td>.484</td>
</tr>
<tr>
<td>Time on vancomycin</td>
<td>2.52 d (0-17)</td>
<td>3 d (0-22)</td>
<td>.0084</td>
</tr>
</tbody>
</table>

This table shows both the clinical and treatment-related outcomes for the study. ID = identification, LOS = length of stay (Koncelik, 2016).
Chapter IV
Discussion

The final section will compare the data that was collected in the results section and compare the different studies to determine if rapid diagnostics can provide faster results, better patient care and hospital management when compared to conventional methods. The following key metrics will be reviewed in detail; time to pathogen identification and susceptibility, antimicrobial stewardship intervention and time to appropriate antimicrobial therapy, mortality, length of stay and hospital costs.

Time to Pathogen Identification and Susceptibility

Rapid diagnostics for pathogen identification and susceptibility are becoming extremely valuable, not only within the clinical laboratory, but also in the hospitals, especially when it is combined with ASP. Allowing clinicians and pharmacists to have potentially lifesaving information days sooner has shown to have a major impact on patient care, hospital costs and hospital quality. This thesis shows that multiple recent studies have proven to have a positive impact on these metrics and hopefully other hospitals will start to adopt both rapid diagnostics and active ASP.

One of the first important metrics to examine was time to pathogen identification and susceptibility. Most of these studies compare a type of rapid diagnostic (MALDI-TOF, FilmArray BCID, Verigene BC-GP or QuickFISH) to conventional methods.
(organism growth, biochemical reactions and growth in the presence of antimicrobials). The only study that did not compare their rapid diagnostic to conventional methods was the FilmArray BCID study by Banerjee et al. (Banerjee, 2015). In this study, they were already running a rapid diagnostic (MALDI-TOF) as their conventional method, however they were not running MALDI from positive blood cultures, but were waiting for colony growth on agar plates prior to testing with MALDI. Therefore some benefits should still be seen on time to pathogen identification and susceptibility but not as great as the other studies.

When comparing all the studies (MALDI-TOF, FilmArray BCID, Verigene BC-GP and QuickFISH) there is a similar trend in which time to pathogen identification is significantly reduced between the pre-intervention and intervention groups; but it was also noticed that FilmArray BCID, Verigene BC-GP and QuickFISH provide even faster results when compared to MALDI. See Figure 2. The reason why MALDI-TOF studies had an increased time to pathogen identification when compared to FilmArray BCID, Verigene BC-GP and QuickFISH is due to the study designs. The MALDI 1 and 3 studies did not perform the assay 24/7; instead the samples were batch and run four times a day, which would explain why the time to pathogen identification is longer. If the samples were not batched, the time to pathogen identification would probably be similar to that of Verigene BC-GP, QuickFISH and FilmArray BCID. The MALDI 2 study inoculated agar media with the blood culture, and then ran MALDI-TOF on the growth, whereas all the other studies ran the assays direct from the positive blood culture.
Figure 2. Time to Pathogen Identification for all Studies

Comparison of pre-intervention group and intervention group for rapid diagnostics reviewed in the study. Time is measured from blood culture positivity to pathogen identification. Maldi 1 (P = <.001), Maldi 2 (P = .001), Maldi 3 (P = <.001), FilmArray BCID (P = <.001), Verigene BC-Gp (no P value was given), QuickFISH (P = <.001).

The time to pathogen identification in the pre-intervention groups all vary due to study designs. The MALDI 1 and 3 studies looked at Gram-negative bacteria, which tend to grow faster than other bacteria and yeast, while the MALDI 2 study looked at all bacteria and yeast species. All the MALDI studies had similar pre-intervention study designs, the blood cultures were inoculated to agar media, and then the isolate was placed on an ID/AST system (Vitek, BD Phoenix or Microscan) which is why the time to pathogen identification is longer. The FilmArray BCID conventional method had blood cultures inoculated onto agar plates and then an isolate was placed onto a MALDI machine, which is why pathogen identification was reported so much sooner than the MALDI experiments. The Verigene BC-Gp study had a very similar design as the MALDI experiments and a comparable time frame. Finally, QuickFISH only looked at
coagulase-negative staphylococci; they inoculated the blood culture onto agar media, but then performed a Staphaurex latex agglutination test and did not place the sample on their ID/AST system.

Time to susceptibility was another important metric in many of these studies because many physicians and pharmacists want to know, not only what organism is causing the infection, but what antimicrobial the organism is susceptible or resistant. Typically optimal therapy will not be started until susceptibility data is provided. Five out of the six studies reviewed time to susceptibility between the pre-intervention and intervention groups. The one study that did not was the QuickFISH study by Koncelik et al. (Koncelik, 2016). The authors did not include this metric because patients with coagulase-negative staphylococci, which is typically considered a contaminant in blood culture bottles, most likely did not have a true infection. A positive coagulase-negative staphylococci result would provide enough information for the antimicrobial stewardship team to determine if the patient needs an antimicrobial (Koncelik, 2016). The remaining five studies did test for susceptibility and the data is shown in Figure 3.
The five different studies had very similar susceptibility times with the pre-intervention groups and showed a significant reduction in time to pathogen susceptibility; however there was a greater reduction with the FilmArray BCID and Verigene BC-GP assays because both of these assays have resistance markers built in, whereas MALDI-TOF does not provide this information. For FilmArray BCID, pathogen identification and susceptibility is built in to one panel, meaning all Gram-positive, Gram-negative and yeast, are included along with three commonly known resistance markers: *mecA* for *Staphylococcus*, *vanA/B* for *Enterococcus*, and KPC for Gram-negatives (BioFire Diagnostics, 2013). The Verigene BC-GP panel only tests for the most prevalent Gram-positive organisms and includes two resistance markers; *mecA* for *Staphylococcus* and *vanA/B* for *Enterococcus* (Nanosphere, 2012). It is good to note that these tests do not
provide true susceptibility data because they are not tested against a panel of antimicrobials, instead they look for the gene that is most likely responsible for causing the antimicrobial resistance and not all resistance markers are included. They do however offer the physicians and pharmacists an idea as to which antimicrobial they should use. The MALDI-TOF studies provided susceptibility data, but not as rapidly as others since organism growth is needed before testing the isolate on the ID/AST system against a panel of antimicrobials to determine susceptibility or resistance.

This significant reduction in pathogen identification and susceptibility is important because this information can now be reported on average one to two days sooner than conventional methods. This will allow the clinicians and pharmacists to adjust therapy sooner, which in turn can have a positive impact on patient care and hospital costs. Leaving patients on inappropriate therapy can have a negative impact on overall health and hospital outcomes. These two key metrics are important to active antimicrobial stewardship teams because adjusting therapy sooner will help minimize adverse events associated with antimicrobials, like \textit{C. difficile} infection and help reduce the risk of increasingly resistant bacteria.

\textbf{Antimicrobial Stewardship Intervention and Appropriate Therapy}

It has been shown that each hour antimicrobial therapy is delayed the risk of patient survival decreases by 7.6\% (Kumar, 2006). This thesis provides more evidence to show that the correct antimicrobial provided at the earliest time will help increase patient survival. As seen from the six studies, conventional methods are not timely and pose a
risk to proper patient management. Decreasing the time to pathogen identification and susceptibility can have a significant impact when selecting appropriate antimicrobial therapy. It is also important to show that active antimicrobial stewardship teams can also help reduce the time to appropriate therapy.

Time to optimal antimicrobial therapy was measured in the three MALDI-TOF and the Verigene BC-GP studies. Each study showed a significant reduction in time when compared to the pre-intervention groups. The MALDI studies showed almost a full two day reduction in time to optimal therapy and Verigene BC-GP was almost a full day. See Figure 4.

Figure 4. Time to Optimal Antimicrobial Therapy
Comparison of pre-intervention group and intervention group for rapid diagnostics reviewed in the study. Time is measured from blood culture positivity to optimal antimicrobial therapy. Maldi 1 (P = .001), Maldi 2 (P = .001), Maldi 3 (P = .004), Verigene BC-GP (no P = .005).
The Perez et al. 2014 study had a 71% decrease in time to optimal therapy between the two groups. In some patient cases, their antimicrobial stewardship team was actually able to optimize antimicrobial therapy before susceptibility testing was finished. This was primarily due to the pathogen identification from MALDI-TOF and patient assessment by the stewardship team. It is interesting to note that a high number of patients in both the pre-intervention and intervention groups were on inactive therapy (72.6% and 64.3%) at the beginning of the study, showing that ASP might be able to help guide antimicrobial therapy as soon as a patient is admitted to help ensure patients are on active therapy as soon as possible. The antimicrobial stewardship team was able to initiate active therapy 57.7 hours sooner with the intervention group (P < 0.001), and over two days sooner than the pre-intervention group (89.7 hours vs. 32 hours). This is important because the prolonged wait for appropriate therapy could have a negative impact on patient care and hospital cost. In this study, the antimicrobial stewardship team only made therapy recommendations with the intervention group. The stewardship team made 136 treatment recommendations to the treating clinicians and 124 (91.2%) were accepted. There were 65 recommendations made once pathogen identification was provided to the ID pharmacist and another 71 once the susceptibility information was provided. Table 7 shows which recommendations were made and at what time point.
Table 7. Antimicrobial Stewardship Interventions for Perez Study

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of recommendations at each timepoint</th>
<th>Total accepted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism identification via MALDI-TOF MS and reported to ID pharmacist (n = 65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escalation or initiation of antibiotic therapy</td>
<td>33</td>
<td>61/63 (96.8)</td>
</tr>
<tr>
<td>Narrowed and/or tailored treatment for isolated pathogen</td>
<td>3</td>
<td>18/21 (85.7)</td>
</tr>
<tr>
<td>Discontinued antibiotics not targeting isolated pathogen</td>
<td>21</td>
<td>26/32 (81.3)</td>
</tr>
<tr>
<td>Optimized regimen based on administration or pharmacokinetics &amp; pharmacodynamics</td>
<td>8</td>
<td>19/20 (95)</td>
</tr>
<tr>
<td>Accepted/Total (%)</td>
<td></td>
<td>124/136 (91.2)</td>
</tr>
</tbody>
</table>

Shows the antimicrobial stewardship interventions at each time point during the study and how many were accepted by the treating physicians (Perez, 2014).

Based on Table 7, it appears that the treating physicians were more comfortable accepting the treatment recommendations when they were escalating or initiating antimicrobial therapy. This may be due to the fact that their patients would be on an antimicrobial or maybe even multiple antimicrobials, which could potentially have a positive impact on the patient’s care. They seemed less comfortable with the recommendation of narrowing antimicrobial therapy or discontinuing a particular antimicrobial which was not needed.

The Huang et al. MALDI study (Huang, 2013) showed a 75% decrease in time to optimal therapy between the two groups. In this study, the antimicrobial stewardship team made 210 treatment recommendations to the treating clinicians, of which 189 (90%) were accepted. The stewardship team made recommendations at three different time points; Gram-stain results, pathogen identification via MALDI-TOF and susceptibility. See table 8 for more information on the recommendations.
Table 8. Antimicrobial Stewardship Interventions for Huang Study

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Gram Stain</th>
<th>Organism Identification</th>
<th>Antimicrobial Susceptibility</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrowed coverage to target the isolated organism</td>
<td>2</td>
<td>22</td>
<td>48</td>
<td>72 (34.3)</td>
</tr>
<tr>
<td>Discontinued therapy targeting organisms not isolated</td>
<td>5</td>
<td>44</td>
<td>19</td>
<td>68 (32.4)</td>
</tr>
<tr>
<td>Initiated or broadened coverage</td>
<td>39</td>
<td>5</td>
<td>9</td>
<td>53 (25.2)</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>17 (8.1)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>54 (25.7)</td>
<td>75 (35.7)</td>
<td>81 (38.6)</td>
<td>210 (100)</td>
</tr>
<tr>
<td>Interventions accepted (%)</td>
<td>49 (90.7)</td>
<td>62 (82.7)</td>
<td>78 (90.3)</td>
<td>189 (90.0)</td>
</tr>
</tbody>
</table>

Table displays the interventions that their antimicrobial stewardship recommended at the different time points and the percentage of recommendations that were accepted by the treating physicians (Huang, 2013).

The treating clinicians accepted the majority of recommendations (96.3%) once the antimicrobial susceptibility data was available compared to the other two time points. This shows that the treating clinicians are more comfortable adjusting therapy once they know the pathogen causing the infection and which antimicrobials are available for treatment.

One challenge that each antimicrobial stewardship team will face is having the clinicians accept the stewardship team’s treatment recommendations. In order for the clinicians to gain trust with the antimicrobial stewardship team, they need to demonstrate a level of leadership, drug expertise and accountability to the hospital and its staff. An education program should also be established in which the antimicrobial stewardship team can educate the hospital workers on antibiotic prescribing, the hospital’s antibiotic
resistant patterns, the nation’s antibiotic resistant patterns and new diagnostic tests available through the laboratories and how the information will be reported out to the clinicians (Pollack, 2014).

The last MALDI study by Perez et al. (Perez, 2013) had a 61% decrease in time to optimal therapy between the two groups. In this study, the antimicrobial stewardship team made 246 treatment recommendations to the treating clinicians and 225 were accepted. The team made treatment recommendations at two different time points; pathogen identification via MALDI and again once susceptibilities were available. The data showed that at the beginning, both groups had a similar number of patients on inactive therapy (22/112 pre-intervention and 16/107 intervention), but having rapid pathogen identification and susceptibility reported out sooner allowed the antimicrobial stewardship team to alter therapy significantly sooner than the pre-intervention group. Twenty-four hours after bottle positivity, the pre-intervention group still had 22 patients on inactive therapy and only five patients in the intervention group. Approximately 48 hours after bottle positivity, the pre-intervention group still had 15 patients on inactive therapy and all patients in the intervention group had been placed on active therapy. This delay in time in appropriate therapy has been shown to lead to increased mortality, hospital costs and patient length of stay (Tumbarello, 2010) (Shorr, 2011).

In the Verigene BC-GP study (Sango, 2013) the authors only looked at patients with Enterococcus infections. The Verigene BC-GP panel has the ability to identify Enterococcus faecalis and Enterococcus faecium as well as the resistance markers that are responsible for vancomycin-resistant Enterococcus (VRE), vanA and vanB. In this study, Sango et al. were able to show a 48% decrease in time to optimal therapy for all
patients compared to conventional methods. The study showed a significant decrease in time to optimal therapy with patients that had vancomycin-resistant enterococci (62.7 hours vs. 31.6 hours) and the Verigene BC-GP assay did provide faster time to optimal therapy for vancomycin-susceptible Enterococcus (VSE), even though it was not significant (40.2 hours vs. 18.6 hours). One reason for a significant decrease in time to optimal therapy for patients with VRE infections is because clinicians would want to wait for the susceptibility results especially when E. faecium is identified because a good majority of E. faecium strains are resistant to vancomycin (67%) (Karlowsky, 2004). With the Verigene BC-GP panel the microbiology lab was able to provide the identification of the pathogen along with the resistance markers that causes VRE. A reason why the time to optimal therapy was not significant for patients with VSE is because E. faecalis strains are normally susceptible to vancomycin (95%) (Karlowsky, 2004) and therefore when the pathogen identification gets reported out as E. faecalis the clinicians feel comfortable determining the optimal therapy before the susceptibility results are reported out. In this study, all of the VSE patients were on appropriate therapy from the beginning because the hospital empiric treatment for this Gram type would be vancomycin. The VRE patients were most likely on inappropriate therapy until pathogen identification and susceptibility were reported. The patients were then escalated to either daptomycin or linezolid (Sango, 2013). Previous studies have shown that VRE is associated with higher mortality rates compared to VSE so providing rapid diagnostics and optimal therapy sooner can help reduce the risk of mortality (DiazGranados, 2005) as well as length of stay and hospital costs (Forrest, 2008).
The FilmArray BCID study (Banerjee, 2015) did not measure time to optimal therapy instead they measured time to first appropriate de-escalation, escalation and administration of active antimicrobials. They also measured how long patients were on therapy to determine if there was a difference between the three study groups (control, FilmArray only and FilmArray + Stewardship). This study was the only one that had three study groups. They measured how rapid diagnostics alone can impact patient management and antibiotic use and also how rapid diagnostics with an active antimicrobial stewardship team can impact patient management compared to a control group. In the FilmArray + stewardship group, the stewardship team made 159 recommendations to treating clinicians of which 78% were accepted in the first 24 hours. The treatment recommendation is lower than the previous studies and could be because the active antimicrobial stewardship team and FilmArray BCID assay was new to the hospital. This study did show a significant decrease in time to the first appropriate de-escalation for the FilmArray + stewardship group when compared to the FilmArray only and control group (21 hours vs. 38 hours vs. 34 hours). It was surprising to see that both the FilmArray groups did not have similar times to appropriate de-escalation. In this case, the treating clinicians seemed to listen to the stewardship teams when antimicrobial de-escalation was recommended, but did not feel comfortable in de-escalating therapy when only results were available and no therapeutic guidance was provided. Removing unnecessary antibiotics is important to antimicrobial stewardship teams and is one of the core elements of antimicrobial stewardship (Pollack, 2014). De-escalating antimicrobials can help reduce future resistant pathogens and also reduce the risk of *C. difficile* infection in the patient (Dellit, 2007). The time to the first appropriate escalation was statistically
significant when the FilmArray + stewardship group was compared to the control (5 hours vs. 24 hours). The FilmArray only group also had a decreased time of six hours. It appears from this study that clinicians are more comfortable escalating therapy then removing therapy from a patient. This also showed that the FilmArray panel provides faster results sooner and therefore antimicrobial therapy could be optimized sooner.

Finally, there was no significant difference in time to administration of an active antimicrobial for patients not on one. The patients in the control group received an active antimicrobial within 11 hours, FilmArray only within six hours and FilmArray + Stewardship within four hours. One reason why there may have been an insignificant difference was because once it was determined that the patient had a positive blood culture bottle the clinicians would then want to start an antimicrobial that would have an effect on the Gram type of the organism found in the bottle. It may have not been the optimal antimicrobial, but it at least had some activity against the class of organisms that were found in the patient, for example the patient may have been placed on a broad-spectrum antimicrobial instead of a narrow-spectrum antimicrobial but both would treat the infection.

The QuickFISH study (Koncelik, 2016) did not measure time to optimal therapy. In this study they showed that rapidly identifying coagulase-negative staphylococci could help clinicians de-escalate unnecessary antimicrobials sooner than conventional methods. Coagulase-negative staphylococci are the most frequently isolated organisms in blood cultures (Karlowsky, 2004) and are typically contaminants that do not require antimicrobial treatment. As mentioned earlier, this study showed a 92% decrease in time to pathogen identification (17.16 hours vs. 1.35 hours) which resulted in a 65% reduction
in days on vancomycin (2.52 days vs. 0.89 days). In this study QuickFISH results were reported with the Gram stain. If the patient was not on an antimicrobial then the clinician would not have to start one which would help reduce the use of unnecessary vancomycin. Once again decreasing the overuse of antimicrobials is one of the core elements of any antimicrobial stewardship team and can help reduce further resistance and other adverse effects such as *C. difficile* infection (Pollack, 2014).

Providing pathogen identification and susceptibility results to treating clinicians and stewardship teams sooner has been shown to have a positive effect on providing optimal therapy faster and better patient survival. Bloodstream infections are one of the hardest infections to determine early appropriate therapy because of the number of organisms that can cause infections and the time it takes to identify the organisms. If appropriate therapy is not started in a timely manner the patients chance of survival decreases significantly. One previous study showed that there was a 17.6 fold decrease in survival when a patient with a bloodstream infection was on an appropriate therapy (Kumar, 2009). Therefore, hospitals need to find better ways to provide actionable results sooner to their staff, and to have stewardship teams’ help in the therapeutic decisions to reduce the time to appropriate therapy and increase patient survival.

**Key Hospital Outcomes (Mortality, Length of Stay and Hospital Costs)**

Providing rapid pathogen identification, susceptibility and appropriate antimicrobial therapy sooner should have an impact on a number of key hospital outcomes, including mortality rates, length of patient stay and hospital costs. In theory
these key metrics should show a reduction if rapid diagnostics and antimicrobial stewardship are being used in the hospitals. This section will look at whether the six studies were able to show a positive impact on these three key metrics.

Only five out of the six studies included mortality data. The QuickFISH study did not measure mortality because their study design included patients with only contaminated blood cultures and were not sick, therefore there was no mortality rate to measure. There are previous first generation PNA FISH studies that have shown significant reduction in mortality for enterococci (Forrest, 2008) and staphylococci (Ly, 2008) when PNA FISH and antimicrobial stewardship were used together.

The remaining five studies provided different mortality rates. Only 2 out of 5 studies showed a significant reduction in mortality between the pre-intervention and intervention groups and the remaining three studies did not (See Figure 5). It is interesting to note that the Verigene BC-GP study (Sango, 2013) had a higher mortality rate for the intervention group compared to the pre-intervention group which was an unexpected. Upon reviewing the study it was clear that it was not designed to capture mortality rates, nor was it their main objective. In this study, they included very sick patients - 20% of the intervention group were deceased within 72 hours of their blood culture turning positive - and these patients could not benefit from the use of a rapid diagnostic test. If the study was designed differently and patients were excluded based on certain criteria, such as other underlying medical conditions, perhaps a decrease in mortality would have been observed.
Figure 5. Patient Mortality Rates
Comparison of pre-intervention group and intervention group for rapid diagnostics and ASP reviewed in the study. MALDI 1 (P = .01), MALDI 2 (P = .021), MALDI 3 (P = .19), FilmArray BCID (P = .74), and Verigene BC-GP (P = .065).

The first two MALDI-TOF studies by Perez et al. 2014 and Huang et al. showed a significant reduction in mortality, but the third MALDI study did not. One reason the third study was not statistically significant was due to the small sample size, however there was a noticeable decrease in mortality between the pre-intervention and intervention groups. The first MALDI study by Perez et al. 2014 was able to adjust their data for multiple confounders (infection source, organism, comorbidities and severity of illness) and found that rapid diagnostics and their active antimicrobial stewardship was an independent predictor for patient survival. These data provide evidence that rapid diagnostics and active antimicrobial stewardship can play a major role in better patient management and hospital outcomes.
The FilmArray BCID study by Banerjee et al. did not show a significant reduction in mortality. This study’s main objective was to determine if FilmArray BCID provided faster pathogen identification and susceptibility compared to their conventional method, which used MALDI-TOF on isolates and to determine if rapid diagnostics alone or with active antimicrobial stewardship made a difference. Due to these objectives a different study design was used and was not tailored to measure differences in clinical or cost outcomes. Banerjee et al. also mentioned that most of their patients were on at least one active antimicrobial at the time of enrollment and were typically over treated which could explain why there was no significant reduction in mortality. Their hospital also had a minimal antimicrobial stewardship program in place before the study began, along with low resistance rates and currently used MALDI-TOF as their conventional method. Results were being reported sooner than typical conventional methods and appropriate antimicrobial therapy could be tailored sooner.

Another key hospital metric that was measured in all the studies was patient length of stay. This is an important metric for hospitals because if they can reduce length of stay, then they can free up a hospital bed for another person, save money for each patient and reduce the risk of hospital acquired infections, for which now hospitals are responsible for paying.

Five out of the six studies showed a significant reduction in length of stay when a rapid diagnostic and active antimicrobial stewardship were in place. See figure 6 for data comparison. The only study that did not show a reduction was the FilmArray BCID study by Banerjee et al. (Banerjee, 2015). In this study, the length of stay seemed to remain constant among the three study groups. As previously stated when discussing mortality,
their study design was not set up to measure differences in length of stay. The institution had a baseline antimicrobial stewardship program in place with the control group and were running a type of rapid diagnostic for pathogen identification and susceptibility and resistance screening. If they were comparing their intervention groups to standard conventional methods and did not have a stewardship program in place like the other studies they would have most likely noticed a significant reduction in length of stay.

Figure 6. Overall Length of Stay
Comparison of pre-intervention group and intervention group for rapid diagnostics and ASP reviewed in the study. Maldi 1 (P = .0001), Maldi 2 (P = .066), Maldi 3 (P = .01), FilmArray BCID (P = .6), Verigene BC-GP (P = .048), and Staph QuickFISH (P = 0.484).

The remaining five studies did show a significant reduction in length of stay. All the studies do have differences in the amount of time their patients spent in the hospital, but it is important to remember that each study looked at a slightly different group of
patients. The MALDI 1 study by Perez et al. 2014 and the Verigene BC-GP study by Sango et al had noticeably longer length of stays for both the pre-intervention group and the intervention group compared to the remaining studies. The Perez et al. 2014 study looked at patients with serious and complicated bloodstream infections caused by antimicrobial-resistant Gram-negative bacteria, which are typically harder to treat. The Verigene study had the highest length of stay for both groups when compared against the other five studies. Their study included all patients, including extremely sick patients, and did not have any exclusion criteria. If this study was conducted in a more selective manner, the length of stay might have been shorter and more comparable to the other studies. The Staphylococcus QuickFISH study had the shortest length of stay for both the pre-intervention and intervention groups. This is once again due to the study design and patient population that was studied. In this study they were looking at patients with coagulase-negative staphylococci positive blood cultures. As mentioned earlier, most of these positive blood culture bottles are due to contaminants during the blood draw and therefore the patient does not have a true bloodstream infection. In this case, they were able to discharge these patients sooner because they were not sick.

The last key metric that many of these studies measured was hospital cost. If rapid diagnostics and active antimicrobial stewardship can reduce unnecessary antimicrobial use, decrease the time to appropriate therapy, lower mortality rates and decrease length of stay then there should be an overall cost savings for the hospital. The one study that did not show a decrease in hospital costs was the FilmArray BCID study by Banerjee et al. Once again their study design was not set up to measure these differences. The MALDI
study by Huang et al. did not measure hospital cost savings so unfortunately we have no data to include. See figure 7 for the cost comparison for the remaining studies.

![Figure 7. Hospital Costs](image)

Comparison of pre-intervention group and intervention group for rapid diagnostics and ASP reviewed in the study. MALDI 1 (P = .002), MALDI 3 (P = .0009), FilmArray BCID (P = .78), Verigene BC-GP (P = .02), and Staph QuickFISH (P = not calculated).

The MALDI studies by Perez et al., the Verigene BC-GP study and the *Staphylococcus* QuickFISH study all showed significant cost savings for the hospital. Unfortunately, none of the studies broke down where the money was saved, therefore no further analysis can be performed. The two MALDI studies calculated overall hospital cost as room and board, pharmacy, radiology and laboratory. The Verigene study did not mention what was included in the hospital cost and the QuickFISH study used the average daily patient cost per day for non-profit Florida hospitals. The QuickFISH study predicted its total yearly savings to be $764,316 just by differentiating *S. aureus* from
coagulase-negative staphylococci with *Staphylococcus QuickFISH* and having an active stewardship program to remove unnecessary vancomycin usage and discharge patients sooner. The Perez et al. 2014 study was able to save a yearly estimated cost of $2.4 million dollars by implementing MALDI-TOF for rapid identification and susceptibility of antimicrobial-resistant Gram-negative bacteria and providing faster results sooner to their stewardship team. The other MALDI study predicted a yearly cost savings of approximately $18 million for the rapid identification of all gram-negative bloodstream infections. If multiple rapid diagnostics are implemented in other hospitals and these hospitals also implemented active antimicrobial stewardship, the amount of money that could be saved for each hospital would greatly increase, along with patient care improvement.

**Conclusion**

After reviewing these six studies it appears that rapid diagnostics for pathogen identification and susceptibility and resistance along with an active antimicrobial stewardship team has shown a decrease in time to pathogen identification and susceptibility, reduction in time to appropriate antimicrobial therapy, which has led to a decrease in mortality, length of stay and hospital costs. These results are very similar to a number of other studies that have been performed and give further evidence that rapid diagnostics and antimicrobial stewardship programs can have a positive effect on both patient management and hospital metrics.
Two other MALDI-TOF studies were able to show that providing rapid pathogen identification sooner had a greater impact on appropriate therapy (Clerc, 2013) (Wenzler, 2016). Another type of rapid diagnostic, Xpert® MRSA/SA BC by Cepheid, which was not discussed here, has shown reduction in unnecessary antimicrobial treatment, faster time to appropriate antimicrobial therapy, reduced length of stay and lower hospital costs when used with antimicrobial stewardship (Parta, 2010) (Bauer, 2010) (Wong, 2012). Another study performed with Xpert® MRSA/SA SSTI, which did not have an active antimicrobial stewardship team in place, did not find a significant decrease in unnecessary antimicrobials between their conventional pathogen and susceptibility method and the rapid diagnostic (Terp, 2014). This shows that an active stewardship team can review the laboratory results, make an informed decision on appropriate antimicrobial therapy and relay this information to the treating clinician. PNA FISH® by AdvanDx is another type of rapid diagnostic that has been around for many years and has shown clinical and economic benefits when used with stewardship teams. These studies have shown faster turnaround time to pathogen identification, which has led to reduction in time to appropriate therapy, decrease in length of stay, reduction in unnecessary antimicrobials, lower hospital costs and reduced mortality (Forrest, 2006) (Ly, 2008) (Forrest, 2008). Another PNA FISH study used the technology, but did not have an active stewardship program. This study did not see the benefits as demonstrated by others (Holtzman, 2011), which again shows that pairing rapid diagnostics with antimicrobial stewardship provides significant benefits.

When dealing with critical bloodstream infections, or other type of pathogen infection, it is important to provide rapid and timely administration of appropriate
antimicrobials. This in turn can help improve patient survival and also help fight the global antimicrobial-resistant pandemic currently being faced. It is important that the antimicrobials currently available are preserved by monitoring their use. By implementing rapid diagnostics and antimicrobial stewardship teams, hospitals can have a positive impact on patient care and more importantly help to prevent and combat the development of multiple antimicrobial-resistant organisms the world is facing.
Bibliography


a rapid microarray assay on blood cultures positive for Enterococcus species. *Journal of Clinical Microbiology*, 51(12):4008-4011.


